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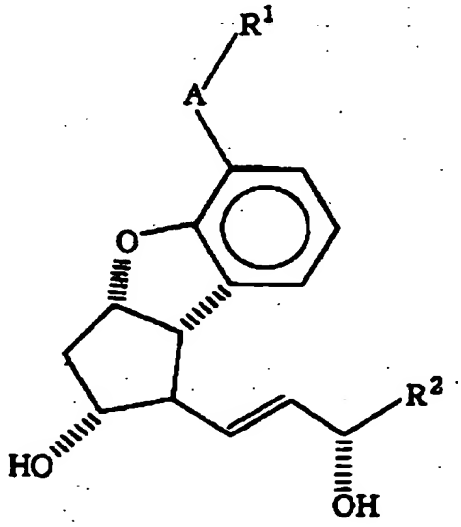
(54) Hair-growing composition containing prostaglandin I 2 derivatives.

(57) A composition for stimulating hair growth is described. The composition comprises as an effective ingredient a 5,6,7-trinor-4 ,8-inter-m-phenylene prostaglandin I_2 derivative of the formula (I) below or a pharmaceutically acceptable salt thereof:



(I)

(wherein

R^1 represents hydrogen, carboxylic group or a functional derivative thereof, $-CH_2OH$ or a pharmaceutically acceptable cation;

A represents

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(i) $-(CH_2)_n-$,
(ii) $-(CH_2)_m-CH=CH-(CH_2)_p-$,
(iii) $-(CH_2)_m-C\equiv C-(CH_2)_p-$ or
(iv) $-CH_2-O-CH_2-$
(wherein n represents an integer of 0 - 3, m and p, the same or different, represent 0 or 1);
R^2 represents
(i) C_5 - C_{10} straight or branched alkyl group,
(ii) $-C_tH_{2t}-OR^3$ (wherein t represents an integer of 1 - 5, R^3 represents C_1 - C_5 straight or branched alkyl group or phenyl group),
(iii) $-C_tH_{2t}-CH=C(R^4)(R^5)$
(wherein t represents the same meaning as mentioned above, R^4 and R^5, the same or different, represent hydrogen, methyl, ethyl, propyl or butyl group), or
(iv) $-C_tH_{2t}-C\equiv C-R^6$
(wherein t represents the same meaning as mentioned above, R^6 represents hydrogen, methyl or ethyl group, and $-C_tH_{2t}$ in (ii), (iii) and (iv) represent straight or branched alkylene group);
wherein said compound of the formula (I) may be d-, l- or dl-form.

BACKGROUND OF THE INVENTION

I. Field of the Invention

This invention relates to a composition for stimulating growth of hair.

II. Description of the Related Art

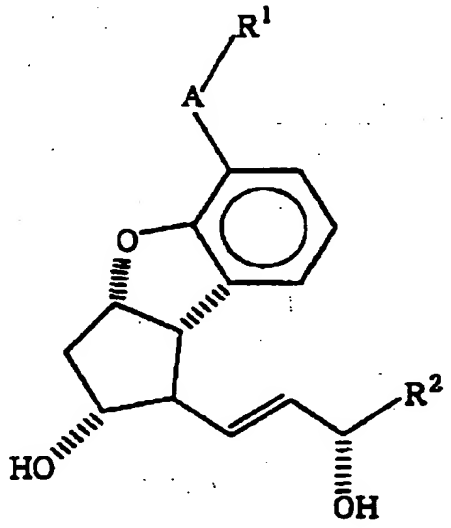
Prostaglandin I_2 (PGI_2, prostacyclin) is a substance known to have strong platelet-aggregation inhibition activity and vasodilating activity. However, since PGI_2 has an unstable exoenol structure, it is extremely unstable even in neutral agueous solution and is easily converted to 6-oxo-PGF1α which has substantially no activities. The instability of PGI_2 is a great problem in using this compound as a pharmaceutical. Furthermore, PGI_2 is unstable in the body and its duration of pharmacological activity is short. To eliminate these drawbacks of PGI_2, PGI_2 derivatives in which the characteristic exoenol ether moiety of PGI_2 is converted to inter-m-phenylene have been proposed in, for example, Japanese Laid-open Patent Application (Kokai) Nos. 57-32277, 57-144276 and 58-124778. However, there is no disclosure or suggestion in these and other published references that these PGI_2 derivatives have activities to stimulate hair growth and so the usefulness for the treatment of alopecia.

SUMMARY OF THE INVENTION

Accordingly, an object of the present invention is to provide a composition for stimulating or promoting hair growth of an animal including human. Another object of the present invention is to provide a new use of the known PGI_2 derivatives.

The present inventors intensively studied to find that the PGI_2 derivatives have activities to stimulate or promote hair growth of animals including human, thereby completing the present invention.

That is, the present invention provides a hair-growing composition comprising a 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I_2 derivative of the formula (I) below or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable vehicle in an amount effective for stimulating growth of hair:



(I)

(wherein

R^1 represents hydrogen; carboxylic group or a functional derivative thereof, $-CH_2OH$ or a pharmaceutically acceptable cation;

A represents

(i) $-(CH_2)_n-$,

(ii) $-(CH_2)_m-CH=CH-(CH_2)_p-$,

(iii) $-(CH_2)_m-C\equiv C-(CH_2)_p-$ or

(iv) $-CH_2-O-CH_2-$

(wherein n represents an integer of 0 - 3, m and p, the same or different, represent 0 or 1);

R^2 represents

(i) C_5 - C_{10} straight or branched alkyl group,

(ii) $-C_tH_{2t}-OR^3$ (wherein t represents an integer of 1 - 5, R^3 represents C_1 - C_5 straight or branched alkyl group or phenyl group),

(iii) $-C_tH_{2t}-CH=C(R^4)(R^5)$

(wherein t represents the same meaning as mentioned above, R^4 and R^5, the same or different, represent hydrogen, methyl, ethyl, propyl or butyl group), or

(iv) $-C_tH_{2t}-C\equiv C-R^6$

(wherein t represents the same meaning as mentioned above, R^6 represents hydrogen, methyl or ethyl group, and $-C_tH_{2t}$ in (ii), (iii) and (iv) represent straight or branched alkylene group);

wherein said compound of the formula (I) may be d-, l- or dl-form.

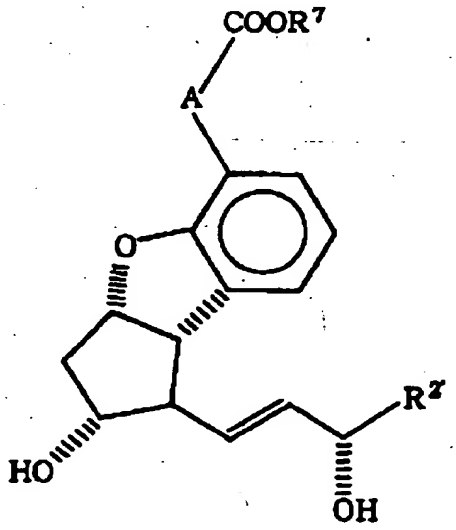
The present invention also provides a use of a 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I_2 derivative of the above-described formula (I) or a pharmaceutically acceptable salt thereof as a hair-growing agent.

The hair-growing composition exhibits high activity to stimulate or promote hair growth in animals including human when orally or parenterally administered.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As described above, the effective ingredient having hair-growing activity in the composition according to the present invention is represented by the above-described formula (I). The functional derivative of carboxylic group for R^1 means the derivative of identical function, such as carboxylic esters. The pharmaceutically acceptable cation for R^1 may be an alkaline metal or an alkaline earth metal such as sodium, potassium or calcium. The compound represented by the formula (I) may be optically active d-form (d-optical isomer) or l-form (l-optical isomer) or may be racemate body (dl-form).

Among the PGI_2 derivatives represented by the formula (I), preferred are those represented by the formula (II):



(II)

(wherein

R^7 represents methyl or ethyl, a pharmaceutically acceptable alkaline metal or alkaline earth metal, or an amine or basic amino acid;

A represents

(i) $-(CH_2)_n-$,

(ii) $-(CH_2)_m-CH=CH-(CH_2)_p-$,

(iii) $-(CH_2)_m-C\equiv C-(CH_2)_p-$ or

(iv) $-CH_2-O-CH_2-$

(wherein n' represents an integer of 1 - 3, m and p represent the same meanings as in formula (I));

$R^{2'}$ represents

(i) C_5 - C_7 straight or branched alkyl group,

(ii) $-C_{t'}H_{2t'}-OR^{3'}$ (wherein t' represents an integer of 1 - 3, $R^{3'}$ represents C_2 - C_4 straight or branched alkyl group or phenyl group,

(iii) $-C_{t'}H_{2t'}-CH=C(R^4)(R^5)$

(wherein t' represents the same meaning as mentioned above, R^4 and R^5 represent the same meanings as in formula (I)), or

(iv) $-C_{t'}H_{2t'}-C\equiv C-R^6$

(wherein t' represents the same meaning as mentioned above, R^6 represents the same meaning as in formula (I), and $-C_{t'}H_{2t'}$ in (ii), (iii) and (iv) represent straight or branched alkylene group);

wherein said compound of the formula (II) may be d-, l-or dl-form.

In the formula (II), the pharmaceutically acceptable alkaline metal or alkaline earth metal for R^7 may preferably be sodium, potassium or calcium. The amine and the basic amino acid for R^7 may preferably be one selected from the group consisting of monomethylamine, dimethylamine, trimethylamine, methylpyperidine, monoethanolamine, diethanolamine, triethanolamine and lysine.

As mentioned above, the PGI_2 derivatives represented by the formula (I) per se are known and the production processes thereof are described in, for example, U.S. Patent No. 4,474,802.

The compounds represented by the formula (I) exhibit hair-growing activities when administered orally or parenterally.

The compounds represented by the formula (I) may usually be administered in a dose of 0.01 - 100 mg/body and 1 - 3 times a day (i.e., 0.01 - 300 mg/body/day).

Although the compounds represented by the formula (I) alone can be administered, they can also be administered together with a pharmaceutically acceptable vehicle.

For oral administration, the active compound may be formulated with a pharmaceutically acceptable vehicle to form a solid composition. Preferred examples of the pharmaceutically acceptable vehicle used for this purpose include starches, lactose, sucrose, glucose, mannitol, calcium carbonate, calcium sulfate and the like. The composition may also contain a binding agent such as starch, dextrin, gum arbicae, tragacanth, methyl cellulose, gelatin, polyvinylpyrrolidone, polyvinyl alcohol or the like; a disintegrator such as starch, polyvinylpyrrolidone, crystalline cellulose or the like; a lubricant such as magnesium stearate, talc or the like; a coloring agent; and a perfume.

The formulation for oral administration may be in the form of tablets, sugar-coated tablets, powder, granules, troches, capsules, balls and syrups.

For parenteral administration, the composition may be formulated into an aqueous sterilized solution for injection (subcutaneous, intravenous, intramuscular, intraperitoneal or the like). The solution may contain other solutes such as sodium chloride or glucose in an amount sufficient to make the solution isotonic.

The concentration of the active ingredient in the composition for oral or parenteral administration is not restricted and may usually be 0.1 ng/ml to 500 µg/ml.

Since the compound of the formula (I) has a stable chemical structure, there is no difficulty in formulating the compound. Thus, in addition to the above-described formulations for oral administration and for injection, the compound may easily be formulated in the form of an absorption-promoting agent, a topical formulation such as ointment, and in the form of a suppository.

The present invention will now be described by way of examples thereof. It should be noted that the examples are presented for the illustration purpose only and should not be interpreted in any restrictive way.

Example

The compound having a structure shown in Table 1 (beraprost) was tested for its hair-growing activity using male New Zealand white rabbits weighing 2 - 3 kg. In Table 1, the groups R^1, R^2 and A in formula (I) are shown.

Table 1

R^1:	-COONa
R^2:	$-CH(CH_3)-CH_2-C\equiv C-CH_3$
A:	$-(CH_2)_3-$

Each group consisted of 3 - 4 rabbits. The hair on the back of each rabbit was shaved. The test compound was administered to each rabbit every day for two weeks and the length of the hair newly grown on the shaved back was measured.

More particularly, for subcutaneous administration, the test compound was dissolved in physiological saline to a concentration of 400 µg/ml and 0.25 ml/kg body weight of the solution was administered to each rabbit at one time every day. For oral administration, the test compound was dissolved in distilled water to a concentration of 400 µg/ml and 0.25 ml/kg body weight of the solution was administered to each rabbit at one time every day. After the oral administration, the solution remaining in the oral administration tube was forced into the body with 3 ml of distilled water. As a control, 0.25 ml/kg body weight of physiological saline was subcutaneously administered. Five or more hairs were collected from five regions in the shaved back and the lengths of the hairs were measured. The results are shown in Table 2.

As shown in Table 2, the test compound significantly increased the length of the newly grown hair when compared with the control group.

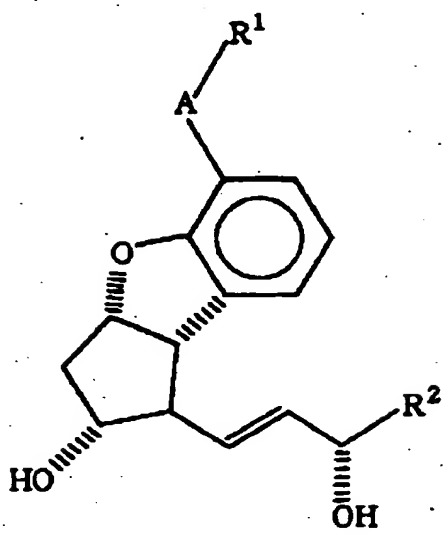
Table 2

Test Compound	Administration Route	Dose	Length of Hair (mm)
Control	Subcutaneous	0.25ml/kg	2.38 ± 0.07
Beraprost	Subcutaneous	0.1 mg/kg	4.54 ± 0.81
	Oral	0.1 mg/kg	3.92 ± 0.24

Claims

1. A hair-growing composition comprising a 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I_2 derivative of the formula (I) below or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable

carrier in an amount effective for stimulating growth of hair:



(I)

(wherein

R^1 represents hydrogen, carboxylic group or a functional derivative thereof, $-CH_2OH$ or a pharmaceutically acceptable cation;

A represents

(i) $-(CH_2)_n-$,

(ii) $-(CH_2)_m-CH=CH-(CH_2)_p-$,

(iii) $-(CH_2)_m-C\equiv C-(CH_2)_p-$ or

(iv) $-CH_2-O-CH_2-$

(wherein n represents an integer of 0 - 3, m and p, the same or different, represent 0 or 1);

R^2 represents

(i) C_5 - C_{10} straight or branched alkyl group,

(ii) $-C_tH_{2t}-OR^3$ (wherein t represents an integer of 1 - 5, R^3 represents C_1 - C_5 straight or branched alkyl group

or phenyl group), (iii) $-C_tH_{2t}-CH=C(R^4)(R^5)$

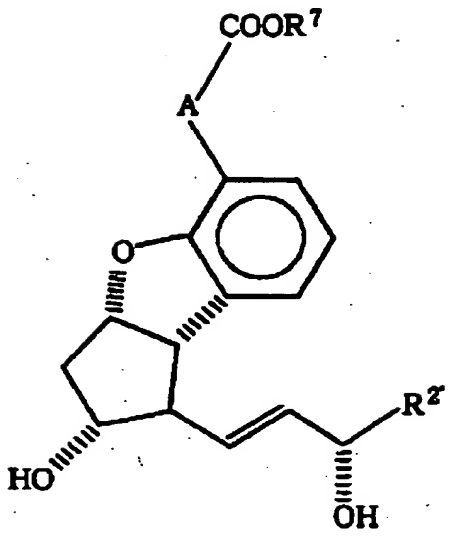
(wherein t represents the same meaning as mentioned above, R^4 and R^5, the same or different, represent hydrogen, methyl, ethyl, propyl or butyl group), or

(iv) $-C_tH_{2t}-C\equiv C-R^6$

(wherein t represents the same meaning as mentioned above, R^6 represents hydrogen, methyl or ethyl group, and $-C_tH_{2t}$ in (ii), (iii) and (iv) represent straight or branched alkylene group);

wherein said compound of the formula (I) may be d-, l- or dl-form.

2. The hair-growing composition according to claim 1, wherein said 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I_2 derivative is represented by the formula (II):



(II)

(wherein

R^7 represents methyl or ethyl, a pharmaceutically acceptable alkaline metal or alkaline earth metal, or an amine or basic amino acid;

A represents

(i) $-(CH_2)_n-$,

(ii) $-(CH_2)_m-CH=CH-(CH_2)_p-$,

(iii) $-(CH_2)_m-C\equiv C-(CH_2)_p-$ or

(iv) $-CH_2-O-CH_2-$

(wherein n' represents an integer of 1 - 3, m and p represent the same meanings as in formula (I));

$R^{2'}$ represents

(i) C_5 - C_7 straight or branched alkyl group,

(ii) $-C_{t'}H_{2t'}-OR^{3'}$ (wherein t' represents an integer of 1 - 3, $R^{3'}$ represents C_2 - C_4 straight or branched alkyl group or phenyl group,

(iii) $-C_{t'}H_{2t'}-CH=C(R^4)(R^5)$

(wherein t' represents the same meaning as mentioned above, R^4 and R^5 represent the same meanings as in formula (I)), or

(iv) $-C_{t'}H_{2t'}-C\equiv C-R^6$

(wherein t' represents the same meaning as mentioned above, R^6 represents the same meaning as in formula (I), and $-C_{t'}H_{2t'}$ in (ii), (iii) and (iv) represent straight or branched alkylene group);

wherein said compound of the formula (II) may be d-, l-or dl-form.

3. The hair-growing composition according to claim 2, wherein said alkaline metal and alkaline earth metal for R^7 is selected from the group consisting of sodium, potassium and calcium, said amine and said basic amino acid for R^7 are selected from the group consisting of monomethylamine, dimethylamine, trimethylamine, methylpyperidine, monoethanolamine, diethanolamine, triethanolamine and lysine.

4. The hair-growing composition according to claim 3, wherein said 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I_2 derivative is beraprost or a pharmaceutically acceptable salt thereof.

5. Use of a 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I_2 derivative of the formula (I) shown in claim 1 or a pharmaceutically acceptable salt thereof as a hair growth-promoting agent.

6. The use according to claim 5, wherein said 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I_2 derivative of the formula (I) is represented by the formula (II) shown in claim 2.

7. The use according to claim 6, wherein said alkaline metal and alkaline earth metal for R^7 is selected from the group consisting of sodium potassium and calcium, said amine and said basic amino acid for

R^7 are selected from the group consisting of monomethylamine, dimethylamine, trimethylamine, methylpyperidine, monoethanolamine, diethanolamine, triethanolamine and lysine.

8. The use according to claim 3, wherein said 5,6,7-trinor-4,8-inter-m-phenylene prostaglandin I_2 derivative is beraprost or a pharmaceutically acceptable salt thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 10 8599

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y D	EP-A-0 084 856 (TORAY INDUSTRIES INC.) * page 1, line 1 - page 2, line 7; claims 1-15 * & US-A-4 474 802	1-8	A61K7/06 A61K31/557
Y	DATABASE WPI Week 8645, Derwent Publications Ltd., London, GB; AN 86-295722 & JP-A-61 218 510 (DAIICHI SEIYAKU KK) 29 September 1986 * abstract *	1-8	
Y	WO-A-8 801 867 (SCHERING AG) * page 5, line 29 - line 33; claims 1-4 *	1-8	
Y D	EP-A-0 060 640 (TORAY INDUSTRIES INC.) * page 13, line 28 - page 14, line 5 * * page 44, line 2 - line 35; claims 1-38 * & JP-A-57 144 276 (...)	1-8	
A	EP-A-0 249 194 (AMERICAN CYANAMID COMPANY) * claims 1-7 *	1-8	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	01 SEPTEMBER 1993	SIATOU E.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
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